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## Phosphorus, Sulfur, and Silicon and the Related Elements

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### Nucleoside Phosphoramidate Analogues with Modification in the Bridging Positions of the Phosphodiester Linkage

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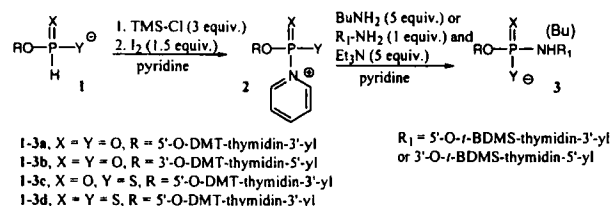
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## Nucleoside Phosphoramidate Analogues with Modification in the Bridging Positions of the Phosphodiester Linkage

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Phosphoramidate modified DNA oligomers<sup>[1]</sup> have recently been shown to have promising properties for antisense/antigene applications. An efficient method, for the preparation of nucleoside P3'→N5' and N3'→P5' phosphoramidates and their thio analogues **3** was developed<sup>[2]</sup>. It consists of the oxidative generation of a pyridine adduct of type **2** of nucleoside metaphosphate from the corresponding nucleoside H-phosphonate, nucleoside H-phosphonothioate or nucleoside H-phosphonodithioate monoester, and its consecutive clean reaction with 5'- or 3'-aminonucleosides in the presence of triethylamine.



To enable efficient oxidation of the nucleoside H-phosphon(othio)ate monoesters to the corresponding metaphosphate intermediates, **1a-c** were converted to their trimethylsilyl diesters *via* treatment with TMS-Cl, prior to I<sub>2</sub> addition. In the instance of H-phosphonodithioate monoester **1d** the silylation with TMS-Cl improved the yields of the product, although no evidence for the formation of silyl ester for **1d** was apparent. In this approach, no phosphorus protecting group is necessary. Yields of isolated dimers range from 69 to 89%. This approach is also applicable for formation of phosphoramidates (and thioanalogues) from alkylamines (*e.g.* butylamine, yields ~70%).

### References

- [1] S. Gryaznov, *et al.*, *Nucleic Acids Res.*, **24**, 1508-1514 (1996).
- [2] I. Kers, J. Stawinski, and A. Kraszewski, *Tetrahedron Lett.*, **39**, 1219-1222 (1998).